

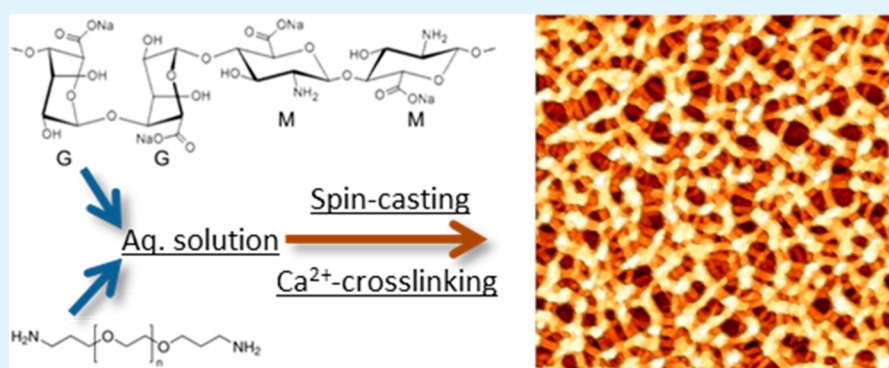
Highly Porous 3D Fibrous Nanostructured Biopolymer Films with Stimuli-Responsive Porosity via Phase Separation in Polymer Blend

Igor Tokarev,[†] Venkateshwarlu Gopishetty,[†] and Sergiy Minko^{*,†,‡}

[†]Department of Chemistry and Biomolecular Science, Clarkson University, Potsdam, New York 13699, United States

[‡]Nanostructured Materials Laboratory, 110 Riverbend Road, The University of Georgia, Athens, Georgia 30602, United States

S Supporting Information



ABSTRACT: The article describes a novel polymer blend system that yields thin films with unique porous nanoscale morphologies and environmentally responsive properties. The blend consists of sodium alginate and amine end-terminated PEG, which undergoes phase separation during film deposition. The blend films can be readily converted into highly porous membranes using facile treatment with a solution containing divalent ions. The resulting membranes are primarily comprised of alginate hydrogel, whereas the PEG phase is removed from the films during exposure to the saline solution, yielding nanometer-sized pores. The alginate gel phase forms a three-dimensional nanostructure which can be best described as a filament or fibrous network. Because such network geometry is untypical of polymer blends in thin films, possible reasons for the observed phase morphology are discussed. Because of ionizable carboxyl groups, the hydrogel membranes demonstrate responsive behavior, in particular a drastic change in their porosity between a highly porous state and a state with completely closed pores in response to changes in the solution pH. The pore-size tunability can be explored in multiple applications where the regulation of material's permeability is needed.

KEYWORDS: alginate, nanostructured thin film, polymer blend, porous material, membrane

INTRODUCTION

Stimuli-responsive polymer thin films have become an area of a growing interest of the scientific community due to a great potential of these materials for a broad range of applications including switchable capture and release, conductivity, mechanical properties, wetting, adhesion, catalytic properties, etc. Porous polymer films represent a distinct, yet important, subclass of responsive multifunctional materials.^{1,2} Thin films with well-controlled nanoscale porosity—most interesting from the point of view of practical applications—are primarily obtained from the multiphase materials by selective removal one of the polymeric phases or a sacrificial colloidal component in hybrid films. A wealth of important applications can be envisioned for them, such as membranes for separation of proteins and macromolecules, templates for nanofabrication, and antireflective coatings.^{3,4}

Responsiveness of the constituent polymers to environmental stimuli renders porous thin films with additional functionalities. Specifically, such multifunctional films could

alter their porosity in response to the pH, ionic strength, electrochemical triggers, and the presence of certain chemicals, and could even be coupled with information-processing circuits based on biochemical reactions.^{5,6} The stimuli-responsive porosity expands the practical capabilities of the materials, making them useful for (bio)sensors, “smart” systems for controlled/triggered release of drugs and various functional molecules, tunable separation membranes, and valves for regulation of mass transport. In this respect, the use of swollen polymeric networks (gels) is advantageous because the gels can undergo large volumetric changes, sometimes reaching several orders of magnitude, without losing the material's integrity.⁷

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Furthermore, many hydrogel materials demonstrate biocompatibility and resistance to biofouling,⁸ and their cross-linked networks can incorporate multiple functional inclusions (e.g., enzymes, catalytic nanoparticles).⁹ We have previously demonstrated that porous hydrogel films (membranes) whose pore size is comparable or larger than the film thickness are capable of changing their porosity between an open highly porous state and a state with completely closed pores.^{9–11} The pores change their size as a consequence of the swelling of the whole body of the film, where the volumetric transition in the responsive gel is triggered by an external stimulus, thus enabling very large amplitude of changes in the material's porosity. Intermediate swelling states are also attainable, enabling a precise control over a pore size—the property that can be used for size-selective transport of biomacromolecules and colloids across the material, as well as for precise regulation of a liquid flow.¹ Filtration applications require inexpensive membranes with relatively narrow pore-size distributions. Thus, there is a need in scalable methods for the fabrication of such membranes using commonly available low-cost polymers.

In our previous publications, we have proposed self-assembly methods based on liquid–liquid phase separation in multi-component solutions comprising a stimuli-responsive cross-linkable polymer and a pore-forming component.^{9–11} The phase separation occurred during spin-cast deposition of polymeric films. For example, monovalent salt was used to disrupt a polyelectrolyte complex of two biopolymers (alginate and gelatin), thus triggering their phase separation in spin-cast films.⁹ Hydrogen bonding between two water-soluble polymers can be also used to delay phase separation, as was demonstrated for the system composed of alginate and poly(vinyl alcohol) (PVA).¹¹ Porous alginate gel films (membranes) were obtained by treatment with an aqueous solution containing calcium ions, which caused an immediate gelation of the alginate phase through the ionic cross-linking mechanism well described by the “egg-box” model¹² and removal of the second pore-forming polymeric component into the solution.

Phase morphologies of immiscible binary homopolymer blends evolve from circular domains of one phase dispersed in the matrix of another through a bicontinuous domain structure to the inverse case of the former.¹³ When a blend is deposited in thin films, its morphology is also affected by interactions of the polymers constituting the blend with the film interfaces. This may lead to the formation of thin wetting layers, whereas most of the material occupies laterally distributed (two-dimensional) domains.¹³ Lateral microstructures comprising circular and bicontinuous domains were specifically observed for the aforementioned alginate-PVA blend.

In this paper, we report our findings of a new binary polymer blend system that yields highly porous thin-film membranes with a three-dimensional (3D) pore structure after extraction of one of the polymer components. The membranes are prepared by spin-casting of aqueous solution mixtures of sodium alginate and O,O'-bis(3-aminopropyl)polyethylene glycol (hereafter denoted as diamine-PEG). The initially miscible-in-solution polymers undergo phase separation at certain stage of the film formation due to loss of the solvent (water) by evaporation. The alginate phase can be stabilized from the subsequent dissolution in aqueous media by ionic cross-linking with divalent calcium ions. The PEG phase is washed away during the cross-linking step producing a porous alginate gel film. The resulting alginate material is biocompatible, biodegradable, and demonstrates pH-responsive properties due to presence of

weak-acid carboxyl functional groups, which makes it interesting for biomedical applications.

It was anticipated that alginate and amine-PEG would demonstrate both hydrogen-bond and electrostatic interactions in water.^{14,15} Polar and ionizable groups of the polymers, such as –OH and –COONa functional groups of sodium alginate and ethereal oxygen and NH₂ end-groups of amine-PEG, should lead to the formation of intra- and intermolecular complexes. These interactions seem to have a profound effect on phase behavior of the blend, as follows from the experimentally observed film morphologies discussed below.

■ EXPERIMENTAL SECTION

Materials. Medium viscosity (≥ 2000 cps for 2% solution at 25 °C, molecular weight is in the range 100 000–350 000 g/mol) sodium alginate from brown algae and diamine-PEG ($M_n = 1500$ mol/g) were purchased from Sigma-Aldrich. Calcium chloride dihydrate (analytical grade) was obtained from J.T. Baker. Highly polished Si wafers were obtained from Semiconductor Processing (Union Miniere, USA).

Membrane Preparation. 1 wt % solutions of sodium alginate and diamine-PEG were prepared by dissolving 0.1 g of each polymer, separately, in 10 mL of Millipore water (18 $\mu\text{S cm}$) at 60 °C. This was followed by mixing the above solutions in various ratios and stirring the resulting mixtures for 1 h at 60 °C. The mixtures prepared this way were used for film deposition by spin-coating. Because of aging, the deposition solution had to be used fresh to guarantee the reproducibility of the results. Films were cast onto smooth solid substrates (Si wafers or glass slides) using the spinning speed of 3000 rpm. Afterward, the dry films, containing a blend of sodium alginate and diamine-PEG were immersed in a 0.3 M calcium chloride solution for 15 min, thoroughly rinsed with Millipore water, and dried in a nitrogen flow. The calcium-ion treatment led to gelation of the alginate component of the films and leaching of diamine-PEG, thereby yielding insoluble films with a porous microstructure (membranes).

To eliminate lift-off of the membranes during swelling experiments, they were chemically immobilized onto solid substrates. To this end, the substrates were first modified with an epoxysilane monolayer according to the procedure described elsewhere⁶ and then the substrates were treated with 1 wt % ethylenediamine to generate a carpet of amine functionalities on the surface. After deposition of membranes on the functionalized substrates, they were annealed at 120 °C overnight to tether the alginate chains to the surface using the reactions of the carboxyl groups with amines. The annealing step did not change the membrane morphology.

Membrane Characterization. A scanning probe microscope (SPM, Dimension 3100, Veeco Instruments, USA), operating in the tapping mode, was employed to visualize the surface topography of the porous alginate membranes in dry and swollen states. A fluid cell was used for in situ experiments. Ultrasharp Si probes with a tip radius of ~ 20 nm, a spring constant of 1.5–6.3 N m⁻¹, and frequency of 63–100 kHz were used for surface characterization. The film thickness in dry and swollen states was evaluated with an SPM scratch test. In this experiment, the film was scratched with a sharp needle to delaminate the polymer material down to the solid substrate. The sample was then scanned around the scratch area to determine a height difference between the polymer film and the substrate, which corresponds to a film thickness.

Infrared (IR) characterization of materials was carried out using a Vector 22 FTIR spectrometer (Bruker Optics).

■ RESULTS AND DISCUSSION

As prepared, 1–4 wt % aqueous solutions containing sodium alginate and diamine-PEG were stable, showing no sign of precipitation. Since the PEG chains bear terminal amino groups capable of electrostatic interactions with carboxyl groups of alginate, diamine-PEG may act as a bifunctional cross-linker that induces interchain cross-linking of alginate. Given that no

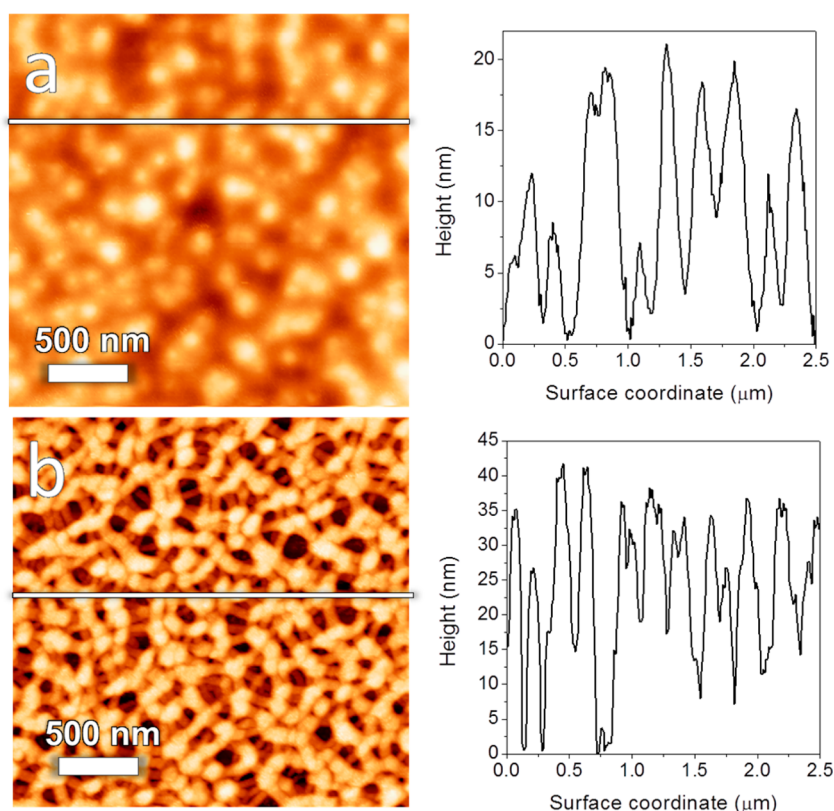


Figure 1. SPM topography images with the corresponding cross-sectional profiles of a thin film of alginate and diamine-PEG (a) before and (b) after treatment with a CaCl_2 solution. The film was prepared from a 1:1 (v/v) solution mixture of 1 wt % solutions of sodium alginate and diamine-PEG. The lines show the locations of cross-sectional profiles.

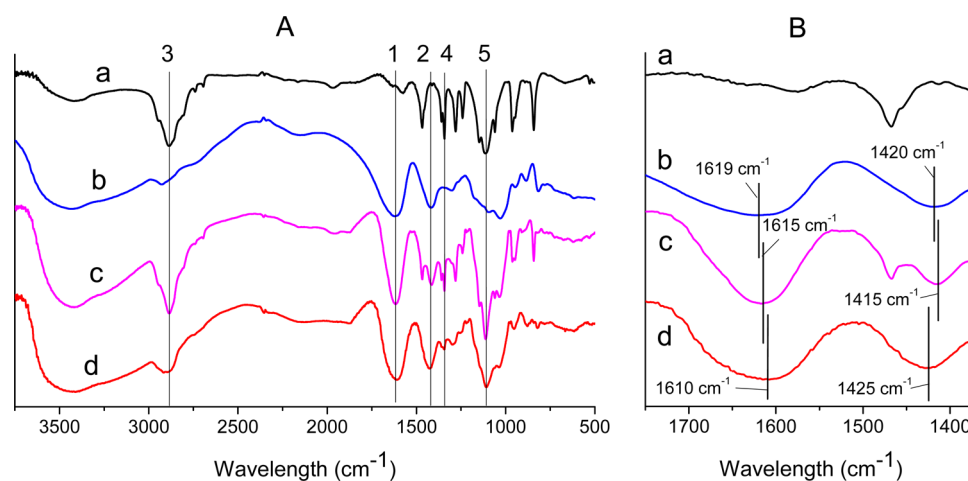


Figure 2. A) FTIR spectra of (a) amine-PEG, (b) sodium alginate, and polymer blend film (c) before and (d) after the treatment with a calcium chloride solution. The vertical lines show the positions of the characteristic bands of sodium alginate at (1) 1619 and (2) 1420 cm^{-1} and amine-PEG at (3) 2887, (4) 1343, and (5) 1140 cm^{-1} . (B) Zoomed-in version of the same spectra highlighting the peak positions of the alginate component.

hydrogel was formed in the solutions we concluded that, in the specified concentration range of polymer solutions, the interchain association was ineffective.

The polymer solutions were used for deposition of thin films by spin-casting. The prepared films were subsequently exposed to a solution containing calcium ions to induce the ionic cross-linking of the alginate component which stabilized the films against dissolution in water. An SPM technique was used to visualize the surface of the films before and after the calcium treatment. The surface microstructures of the as-prepared films,

shown specifically in Figure 1a for the film prepared from a 1:1 (v/v) mixture of 1 wt % solutions of alginate and diamine-PEG, reveal bumpy morphologies, being a sign of phase separation between the polymers in the films. The phase SPM images (see Figure 1S in the Supporting Information) show a clearly visible contrast between the phases, originating from very different mechanical properties of alginate and amine-PEG constituents. Phase separation of blends of sodium alginate and PEG in bulk was also reported elsewhere.¹⁵

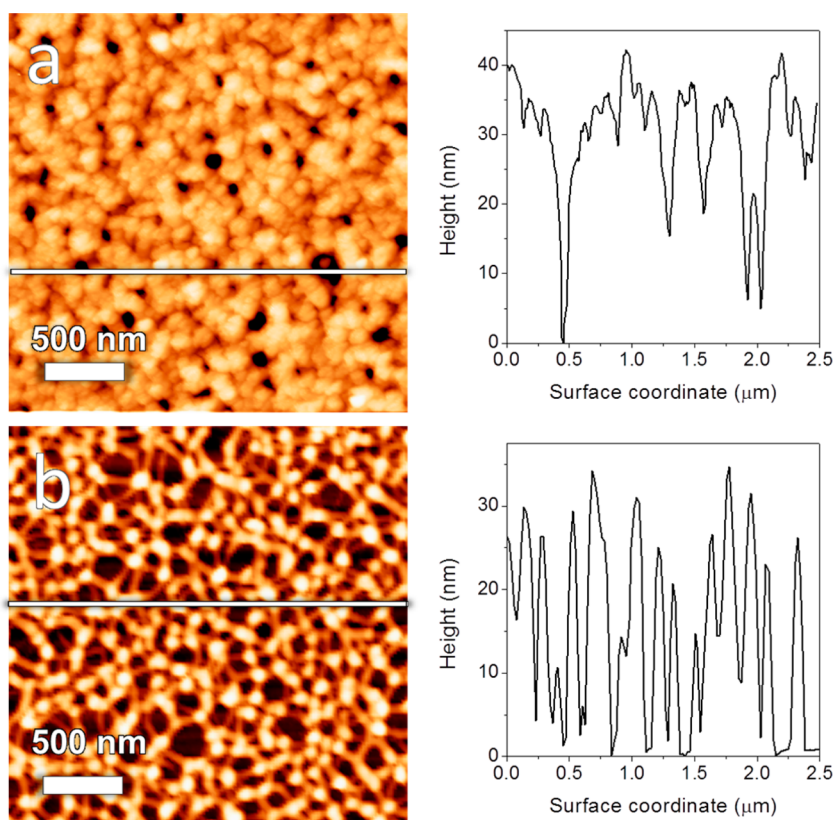


Figure 3. SPM topography images with the corresponding cross-sectional profiles of alginate gel membranes prepared from the blends of 1 wt % solutions of alginate and diamine-PEG mixed in the volume ratios of (a) 2:1 and (b) 1:2. The lines show the locations of cross-sectional profiles. The average pore diameters measured at the half pore depth of the membranes are 74 ± 27 and 170 ± 53 nm (b).

We observed striking changes in the morphology of the films after exposure to the calcium solution while the film thickness decreased by less than 10%. Thus, the SPM image of the aforementioned 1:1 alginate-PEG film after the calcium treatment (Figure 1b) reveals a highly porous morphology with a three-dimensional (3D) microstructure. The film thickness (by the scratch test) and the pore size (as measured by the SPM tip at the half pore depth) are found to be ca. 35 nm and 137 ± 40 nm, respectively.

The drastic transformation of the film's morphology from continuous to highly porous occurring upon the calcium treatment provides evidence for phase separation between alginate and diamine-PEG in the films, where the alginate phase gets stabilized by calcium-ion cross-links and the PEG phase dissolves in water, yielding pores. This interpretation of the morphological transformations is also corroborated by the analysis of FTIR spectra of the material. The characteristic absorption bands of sodium alginate and diamine-PEG allowed us to distinguish these polymers in the spectra (Figure 2). For instance, we can select alginate's characteristic bands at 1619 and 1420 cm^{-1} , which correspond to asymmetric and symmetric stretching vibrations of the COO^- group, respectively.¹⁶ In the case of diamine-PEG, the absorption bands at 2887 cm^{-1} (CH stretching), 1343 cm^{-1} (CH bending), and 1140 cm^{-1} (CO bending) are particularly useful for identifying this polymer component in the blend.¹⁴ Thus, the characteristic bands of both polymers are observed in the spectra of the blend film (Figure 2). Both bands of sodium alginate in the blend red-shifted to 1615 and 1415 cm^{-1} , hinting on possible interactions (hydrogen bond and electro-

static) with diamine-PEG.¹⁴ The infrared spectrum of the blend film after exposure to calcium solution underwent drastic changes. The intensities of the PEG's bands at 2888 and 1344 cm^{-1} decreased significantly after the calcium treatment, implying that a greater part of diamine-PEG was washed away from the blend film. The alginate's COO^- bands experienced shifts to 1610 and 1425 cm^{-1} that were due to the polymer complex disruption and calcium ion cross-linking.¹⁷

Figure 3 shows the surface morphologies of the blend films prepared from solutions with different ratios of sodium alginate and amine-PEG after the Ca-ion treatment. It is apparent that an increase in the content of the pore-forming amine-PEG leads to an increase in the pore size and overall porosity of the resulting alginate gel films. Such porous thin films will be referred to later in the text as membranes to distinguish them from the untreated continuous films. This experiment demonstrates that, by changing the polymer blend composition, it is possible to obtain ~ 30 – 40 nm-thick membranes with the average pore sizes ranging from 74 nm (for the 2:1 alginate–amine-PEG ratio) to 170 nm (for the 1:2 ratio). As for thin-film membranes prepared by phase separation of the polymer blend, a pore structure is quite uniform with the size distribution of ca. 30% of the average pore diameter.

Careful examination of the SPM images in Figure 3 reveals unusual phase segregated morphologies for homopolymer blend thin films. Contrary to typically observed two-dimensional circular and bicontinuous domain microstructures, the alginate–amine-PEG films demonstrate a 3D microstructure, in which the alginate phase forms a well-defined filament network;

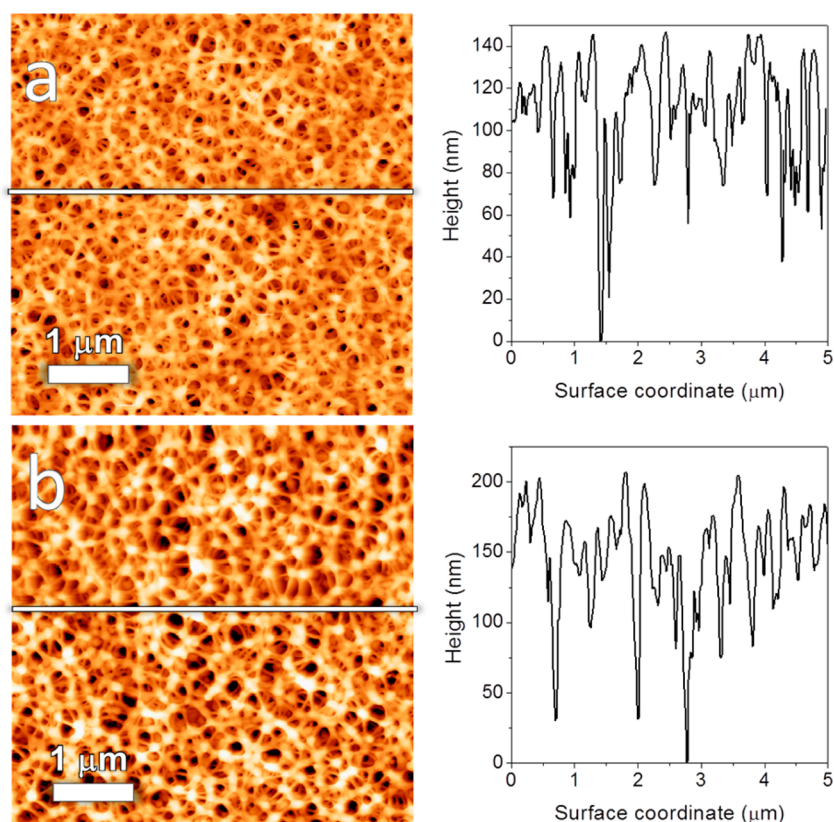


Figure 4. SPM topography images with the corresponding cross-sectional profiles of alginate gel membranes prepared from a 1:1 (v/v) solution mixture of sodium alginate and diamine-PEG with the total polymer concentration of (a) 2 wt % and (b) 3 wt %. The lines show the locations of cross-sectional profiles.

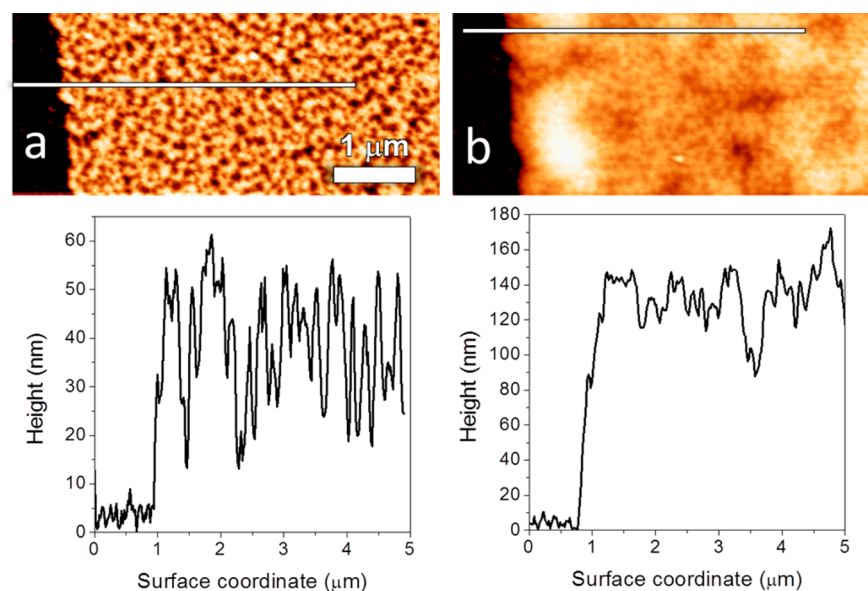


Figure 5. In situ SPM topography images with the corresponding cross-sectional profiles of alginate gel membranes (same as in Figure 1b) immersed in water at (a) pH 2.0 and (b) pH 4.6. The lines show the locations of cross-sectional profiles.

such a filament network becomes apparent after the dissolution of amine-PEG. Interestingly, the filament morphology persists for different blend ratios, even when amine-PEG becomes the dominant component of the blend (see Figure 3b). The formation of the 3D structure could be a result of a complex interplay of hydrogen-bond and electrostatic interactions between alginate and diamine-PEG. These interactions may

improve the compatibility of the polymers, and thereby, delay the moment when the phase separation occurs during concentration quenching. On the basis of the experimental results, it is reasonable to speculate that the alginate-diamine-PEG system behaves as a polymer blend in the weak segregation limit (or a partially miscible blend), characterized by a low interfacial tension between the alginate-rich and

diamine-PEG-rich phases. The experimentally observed small size of the phase-segregated domains could be a combined result of delayed phase separation, a low interfacial tension between the phases, and slow demixing of the polymers because of the increasing viscosity of the solution since both polymers demonstrate gelling properties.

It is noteworthy that the alginate filament network seems to be strongly deformed in the vertical direction. It can be concluded from the fact that lateral pore dimensions are larger than a membrane thickness. Such vertical contraction of the microstructure occurs likely during the late stages of the film formation by spin-casting. Specifically, solvent evaporation from the film seems to cause the vertical deformation of phase-segregated domains, whereas changes in in-plane dimensions of the domain are largely impeded because of lateral constraints imposed by a substrate. An increase in the concentration of the casting solution leads to an increase in the thickness and pore size of membranes but does not alter their surface morphology (Figure 4).

Thus, the membrane thickness rapidly grows from 35 to 135 nm and then to 330 nm as the concentration of the casting solution rises from 1 to 2 wt % and then to 3 wt %, respectively. Unlike the thickness, the average pore size was substantially less impacted, increasing moderately from 137 nm for the 1 wt % solution to 210 nm for the 3 wt % solution. In the 3 wt % membranes (Figure 4b), the average pore size became smaller than the film thickness. The pores are continuous in the thicker films as concluded from the fact that similar porous morphologies were observed on the both sides of the membrane (to visualize the reversed side the membrane was flipped upside down by contact transfer; see Figure 2S in the Supporting Information).

The Ca^{2+} -cross-linked alginate membranes were stable when immersed in water at different pH values below pH 8. Furthermore, in situ SPM measurements in a fluid cell (Figure 5) showed that the membranes underwent pronounced pH-dependent swelling which had in turn a strong impact on the their porosity. The SPM scratch analysis was employed to determine the thickness of a membrane in the swollen state. A ratio of the thickness in the swollen state to that of the dry membrane was used to characterize a swelling degree of the material. The membrane had the lowest swelling degree of 1.3 at pH 2.0 and reached the highest swelling state of 4.6 at pH 6.0. Outside of this pH window, no significant changes in the swelling degree were identified. This swelling behavior was completely reversible and similar to what we observed for the previously studied alginate-based systems.^{9,11} All these materials showed a sharp swelling transition occurring in a pH range of 4 to 5 with the inflection point at ca. pH 4.5. The latter value is close to the pK_a value of alginic acid (reported to be between 3.4 and 4.4).¹⁸ Thus, the pH-dependent swelling behavior can be attributed to the ionization of carboxyl groups of alginate. In our previous work,⁹ we showed that some fraction of the carboxyl groups was not involved in ionic cross-linking (i.e., not bound with calcium ions) and remained in the ionizable sodium salt form. The ionization of these unbound weak-acid groups above the pK_a value generates a strong osmotic-pressure component which drives the membrane swelling. The ~1.3-fold swelling at low pH values, where the carboxyl groups are practically not ionized, can be rationalized by hydration of polar hydroxyl groups of alginate.

As mentioned above, the pH-driven swelling of the alginate gel membranes caused profound changes in the material's

porosity. In the case of the membrane shown in Figure 1b, the minor swelling at pH 2.0 did not alter substantially the porosity compared to the dry state (Figure 5a). On the other hand, an increase of the pH to just 4.6 (the inflection point) caused partial ionization of the in-bound sodium carboxylate groups which was sufficient to swell the membrane's walls to the extent when all the pores became closed (Figure 5b). The contraction of the pores upon swelling is a consequence of the lateral constraints in a membrane immobilized onto a solid support, where the expansion of the swelling gel walls is allowed only in the vertical direction and into the pore interior. Obviously, the membranes' pores remain closed at the pH values above 4.6. The property of the membrane to rapidly change its porosity in response to a pH trigger can be utilized for designing "smart" materials and devices, such as tunable filtration membranes, triggered drug release systems, and flow valves. It has been found that the calcium cross-linked alginate films gradually lose their integrity upon continuous washing with buffer solutions because of the exchange of Ca^{2+} -ions with monovalent ions from the solution. Thus, for certain applications, the ionic cross-links can be substituted with covalent ones. Such covalently cross-linked membranes preserve their pH-responsiveness.

CONCLUSIONS

We demonstrated a homopolymer system composed of sodium alginate and amine-PEG which shows a phase segregated morphology in thin films. The same morphology persists for different ratios of the polymers in the mixture, unlike the classical polymer blends where the morphology undergoes through distinct states as the composition changes. Another important characteristic, which distinguishes the present system from classic blend films, is a relatively small size of phase-segregated domains. That behavior of the studied blend could be a result of electrostatic and hydrogen-bond interactions between alginate and amine-PEG, which likely improve the compatibility of the polymers, delaying the phase separation during the concentration quenching, and reduce the interfacial tension between the phases. However, other unanticipated yet factors cannot be ruled out. An important from a practical point of view feature of the alginate-amine-PEG system is the ability to cross-link the alginate phase and remove the amine-PEG phase, which transforms the blend film into a highly porous membrane. The porous structure allows us to visualize the morphology of the alginate gel phase which forms a 3D filament network. The alginate membrane demonstrates stimuli-responsive behavior, switching between the highly porous state and the state where all the pores are closed in response to the solution pH, which can be explored in the applications that require the regulation of mass transport.

ASSOCIATED CONTENT

Supporting Information

SPM topography and phase images of an as-prepared thin film of alginate and diamine-PEG (no treatment with a CaCl_2 solution) and SPM topography image with the corresponding cross-sectional profile of alginate gel membrane that was transferred onto the surface of a polycarbonate track-etch filter. This material is available free of charge via the Internet at <http://pubs.acs.org>.

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: E-mail:sminko@uga.edu.

Notes

The authors declare no competing financial interest.

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